



Systematic Evidence Map (SEM) to Characterize Available Evidence for 9000 PFAS

Kristina Thayer
CPHEA/CPAD
Office of Research and Development

Executive Meeting | Board of Scientific Counselors
September 29-30, 2021

The views expressed in this presentation are those of the author(s) and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

- Use systematic review methods to identify and summarize animal bioassay and epidemiological evidence for ~9000 PFAS
 - Create a repository that is easily updated, web-based, and shareable
 - Focused on PFAS structures and substances listed in EPA CompTox Chemicals Dashboard
- Specific uses:
 - Identify *in vivo* evidence to inform CTE efforts to characterize PFAS library
 - Characterize data gaps and key research needs
 - Be positioned to quickly address new PFAS assessment needs



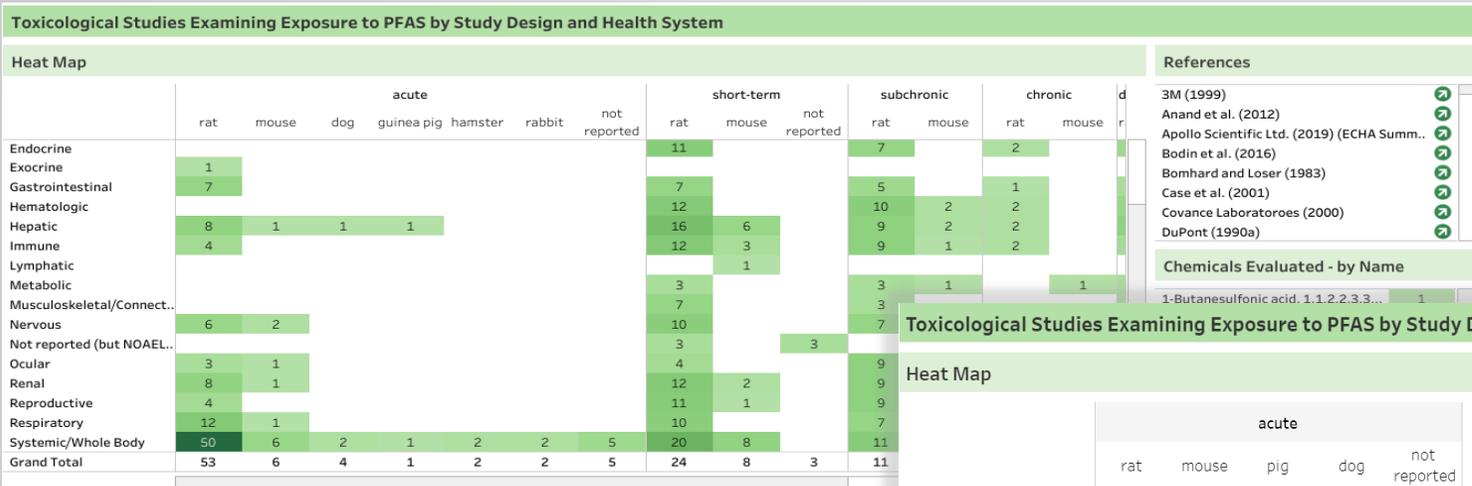
Approach

- Systematic review methods used to search for, screen, and evaluate the relevant literature
 - Use machine-learning and automated approaches to develop search strategies
- Searches initiated in batches as they were identified of interest (“PFAS 150”, “PFAS 430”, “PFAS 9000”)
 - List of 9,000 PFAS substances and structures includes most of the chemicals in the EPA CompTox chemicals dashboard (https://comptox.epa.gov/dashboard/chemical_lists/PFASSTRUCT)
- Study methods and findings summarized (“data extraction”) and the results made available online as downloadable and interactive visual formats
- ADME studies*, PBPK models*, *in vitro* studies, and exposure-only human studies being tracked as supplemental material
- Cross-checked reference lists with other resources (e.g., ATSDR drafts)

*ADME = absorption, distribution, metabolism, and elimination; PBPK model = physiologically based pharmacokinetic model 3



Interactive Displays: Inventory

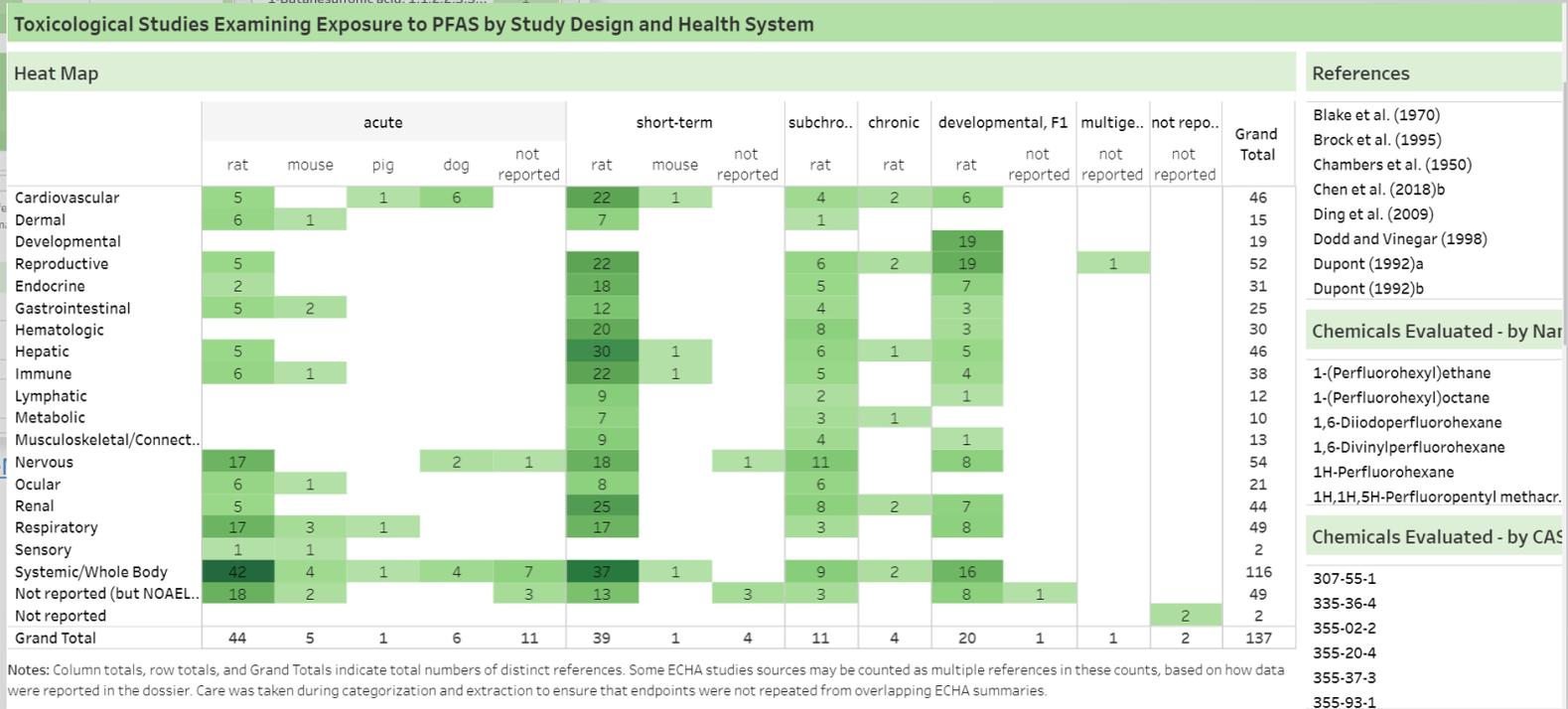


Notes: Column totals, row totals, and Grand Totals indicate total numbers of distinct references. Some ECHA studies sources may be counted as multiple references if they were reported in the dossier. Care was taken during categorization and extraction to ensure that endpoints were not repeated from overlapping ECHA summaries.

Study Details

Health System	Study Design	Route	Species	Sex	Short Citation
Cancer	chronic	inhalation	rat	both	Haskell Laboratories (1995) Malley et al. (1998)
Cardiovascular	acute	inhalation	rat	male	DuPont (1992b)
			dog	male	DuPont (1992d)
			not reported		Unnamed Report (1992b) (ECHA Summary) DuPont (1994)

<https://public.tableau.com/app/profile/literature.inventory/viz/PFAS-150Evidence>



<https://public.tableau.com/app/profile/laura.carlson/viz/BDRP2021posterLMC/AnimalStudies>

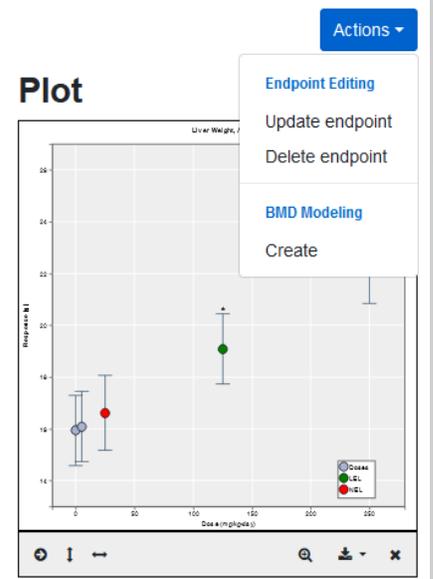


Interactive Displays: Extraction

Chemical	Endpoint	Study	Animal Description	Route	Exposure Duration	
6:2 Fluorotelomer alcohol	Liver Weight, Absolute	Mukerji et al. 2015	P0 Mouse, Crl:CD-1(ICR)BR (♀)	oral gavage	14d pre-mating, 14d mating, gestation, lactation	
			P0 Mouse, Crl:CD-1(ICR)BR (♂)	oral gavage	109 d (pre-mating-sacrifice)	
		Serex T et al. 2014	Rat, Crl:CD(SD) (♀)	oral gavage	90 d	
			Rat, Crl:CD(SD) (♂)	oral gavage	90 d	
			Unnamed report (2005a) (ECHA summary)	Rat, Crl:CD(SD) (♂/♀)	oral gavage	28 d
	Liver Weight, Relative	Mukerji et al. 2015	P0 Mouse, Crl:CD-1(ICR)BR (♀)	oral gavage	14d pre-mating, 14d mating, gestation, lactation	
			P0 Mouse, Crl:CD-1(ICR)BR (♂)	oral gavage	109 d (pre-mating-sacrifice)	
		ECHA, 2007, 5701160	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)	
			Rat, Crl:CD(SD) (♀)	oral gavage	90 d	
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)	
6:2 Fluorotelomer methacrylate	Liver Weight, Absolute	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)	
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)	
	Liver Weight, Absolute, Recovery	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)	
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)	
	Liver Weight, Relative	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)	
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)	
	Liver Weight, Relative, Recovery	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)	
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)	
	Trifluoroacetic acid	Liver Weight, Absolute	Unnamed Report (2010a) (ECHA Summary)	P0 Rat, Crl:CD(SD)IGS BR (♀)	oral gavage	GD 6-19
			Unnamed Report (2012b) (ECHA Summary)	P0 Rat, Crl:CD(SD)IGS BR (♀)	oral gavage	up to 57 d (pre-mating-lactation)
Saillenfait et al. 1997			P0 Rat, Crl:CD(SD)IGS BR (♂)	oral gavage	38 d (pre-mating-termination)	
			P0 Rat, Sprague-Dawley (♀)	oral gavage	GD 10-20	
			F1 Rat, Sprague-Dawley (♂/♀)	oral gavage	GD 10-20	
Liver Weight, Relative		Unnamed Report (2016a) (ECHA Summary)	Rat, Wistar Rj:Wi (lops Han) (♀)	oral diet	90 d	
			Rat, Wistar Rj:Wi (lops Han) (♂)	oral diet	90 d	
		Unnamed Report (2012b) (ECHA Summary)	P0 Rat, Crl:CD(SD)IGS BR (♀)	oral gavage	up to 57 d (pre-mating-lactation)	
			P0 Rat, Crl:CD(SD)IGS BR (♂)	oral gavage	38 d (pre-mating-termination)	
			Saillenfait et al. 1997	P0 Rat, Sprague-Dawley (♀)	oral gavage	GD 10-20
Unnamed Report (2016a) (ECHA Summary)	F1 Rat, Sprague-Dawley (♂/♀)	oral gavage	GD 10-20			
	Rat, Wistar Rj:Wi (lops Han) (♀)	oral diet	90 d			
Rat, Wistar Rj:Wi (lops Han) (♂)	oral diet	90 d				

Liver Weight, Absolute Endpoint Details

- Endpoint name: Liver Weight, Absolute
- System: Hepatic
- Organ: Liver
- Effect: Clinical Observation
- Effect subtype: Organ Weight
- Diagnostic description: Liver, Weight
- Observation time: 90 d
- Data reported?: ✓
- Data extracted?: ✓
- Values estimated?: -
- Location in literature: Table 5
- Expected response adversity direction: ---
- NEL: 25 mg/kg-day
- LEL: 125 mg/kg-day
- Monotonicity: --
- Trend result: not reported
- Results notes: "Following 90 days of dosing, effects on organ weights were present in the testes, liver and kidney of males (Table 5) and in livers and kidneys of females (Table 6)..."



Dataset

Dose (mg/kg-day)	Number of Animals	Response (g)	Standard Deviation
0	10	15.94	1.9
5	10	16.09	1.9
25 ^a	10	16.62	2.02
125 ^{b,c}	10	19.09	1.89
250 ^b	8	22.84	2.39

^a NEL (No effect level)
^b Significantly different from control (p < 0.01)
^c LEL (Lowest effect level)

Legend

- ++ Good (metric) or High confidence (overall)
- + Adequate (metric) or Medium confidence (overall)
- Deficient (metric) or Low confidence (overall)
- Critically deficient (metric) or Uninformative (overall)
- NR Not reported
- N/A Not applicable
- * Multiple scores exist
- ▲ Bias away from null

	BioDynamics 1991	Bodin J et al. 2016	Case, York, and Christian 2001	Covance 2000	Dupont 1991	Dupont, 1991, 5380491	ECHA, 1976, 6299236	ECHA, 1992, 6299232	ECHA, 1995, 6299219	ECHA, 2001, 6299228	ECHA, 2001, 6299250	ECHA, 2007, 5701160	ECHA, 2011, 5701148	Feng M et al. 2015	Grossman, Mispagel, and Bowen 1992	Haskell Laboratory 1995	Ladics et al. 2008	Malley et al. 1996	Malley et al. 1998	Mukerji et al. 2015	Mychreest E, Mur	O'Connor	Pe
Reporting	++	+	++	+	++	++	-	-	-	+	-	+	-	+	++	++	++*	++	+	++	++	+	++
Allocation	+	+	NR	++	++	++	NR	NR	+	+	NR	+	+	++	++	++	++	++	++	++	++	++	++
Blinding	▲ NR	NR	NR	NR	++*	NR	NR	NR	+	++	NR	NR	NR	++*	NR	NR	++*	NR	++*	NR	NR	NR	+
Confounding/Variable Control	++	++	++	++	++	++	-	NR	++	+	++	+	++	++	++	++	++	++	++	++	++	++	++
Selective Reporting/Attrition	++	+	+	+	++	++	+	+	+	+	+	++	+	++	+	++	+	++	+	++	+	++	+
Exposure Characterization	++	+	++	+	++	++	-	NR	-	+	-	-	+	+	--	+	++	++	++	++	+	+	++
Study Design Applicability	+	++	++	++	++	++	-	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++	++
Outcome Assessment	-	++*	++*	++*	++	++*	-	-	++	-	-	++	-	+	++	++	++*	++	+	+	++	+	++
Results Presentation	++	++*	++*	++*	++	++*	-	++*	++*	++*	++*	++*	++*	++*	++*	++*	++*	++*	++*	++*	++*	++*	++*
Overall confidence	+	++	+	+	++	+	-	-	+	+	-	-	-	--	++*	++*	++*	++*	++*	++*	++*	++*	++

Study evaluation: Grossman, Mispagel, and Bowen 1992, 3981622

Grossman, Mispagel, and Bowen 1992, 3981622

Reporting Quality

Reporting quality

Adequate

Adequate. The focus of this study is the tissue distribution and elimination of the tested substance following dietary administration. Body weight, food consumption, and clinical signs were also assessed. Sufficient information is provided for test species/strain/sex/age, exposure methods, diet and husbandry conditions, frequency of exposure. There are some reporting deficiencies with respect to experimental methods and results. Body weight data for the post-treatment phase were not presented; the study indicated that these data could not be statistically analyzed because of small control group size. Food consumption data for post-treatment period also were not presented (it is unclear whether it was measured). Clinical signs were evaluated, but were not discussed in the methods section. In addition, although the numbers of animals/group/sacrifice timepoint were reported, sample sizes aren't noted in the figures.

Selection and Performance

Allocation

Adequate

Adequate. Authors report that "rats were randomly divided" into groups, but provides no further details.

Observational bias/blinding

body weight, food consumption

NR

Not reported

Not reported (interpreted as Adequate). Body weight, food consumption. The study did not indicate whether examiners were blinded to animals' exposure status for these outcomes. Because these outcomes are objective, the concern for potential bias is low.

clinical signs

NR

Not reported

Not Reported (interpreted as Deficient). Clinical signs. The report did not indicate whether examiners were blinded to animals' exposure status for this outcome. Because this outcome can be subjective, assessor blinding is important.

Close

6



Findings to Date

- Many PFAS are data poor
 - PFAS 150: 136 animal studies for 35 PFAS, 166 human studies for 11 PFAS
 - PFAS 430: 341 unique chemicals searched that were not included in prior search; 142 had data
 - PFAS 9000: 9,266 PFAS chemicals were searched; 416 have records
- Data extraction has been extended to shorter-term studies (<1 month)
- When a specific PFAS is identified as of interest, additional higher level of effort steps are taken to identify evidence (i.e., availability of CBI studies)
- Very few inhalation toxicity studies available
 - ORD exploring approaches for extrapolating from oral administration studies

- PFAS 150: Manuscript submitted September 2021
- PFAS 430: Manuscript planned for FY22
 - 119 animal bioassay studies undergoing extraction and study evaluation; 48 human studies identified
- PFAS 9000: Screening underway
 - 26,000 records being screened at title and abstract level
- Overall goal is to create a single repository that can be readily updated



Contributors

- Laura M. Carlson, CPHEA/HEEAD
- Michelle Angrish, CPHEA/CPAD
- Elizabeth G. Radke, CPHEA/CPAD
- Brittany Schultz, CPHEA/HEEAD
- Andrew Kraft, CPHEA/CPAD
- Avanti Shirke, CPHEA/CPAD
- Richard Judson, CCTE/BCTD
- Grace Patlewicz, CCTE/CCED
- Robyn Blain, ICF International Inc.
- Cynthia Lin, ICF International Inc.
- Nicole Vetter, ICF International Inc.
- Courtney Lemeris, ICF International Inc.
- Pamela Hartman, ICF International Inc.
- Heidi Hubbard, ICF International Inc.
- Xabier Arzuaga, CPHEA/CPAD
- Allen Davis, CPHEA/CPAD
- Laura V. Dishaw, CPHEA/CPAD
- Ingrid Druwe, CPHEA/CPAD
- Hillary Hollinger, CPHEA/HEEAD
- Ryan Jones, CPHEA/HEEAD
- J. Phillip Kaiser, CPHEA/CPAD
- Lucina Lizarraga, CPHEA/CPAD
- Pamela Noyes, CPHEA/CPAD
- Michele Taylor, CPHEA/CPAD
- Andrew J. Shapiro, CPHEA/HEEAD
- Antony J. Williams, CCTE/CCED
- Kristina A. Thayer, CPHEA/CPAD

Supported by Health and Environmental Risk Assessment